ClinicalEvidence

Nausea and vomiting in early pregnancy

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ABSTRACT

INTRODUCTION: More than half of pregnant women suffer from nausea and vomiting, which typically begins by the 4th week and disappears by the 16th week of pregnancy. The cause of nausea and vomiting in pregnancy is unknown, but may be due to the rise in human chorionic gonadotrophin concentration. In 1 in 200 women, the condition progresses to hyperemesis gravidarum, which is characterised by prolonged and severe nausea and vomiting, dehydration, and weight loss. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatment for nausea and vomiting in early pregnancy? What are the effects of treatments for hyperemesis gravidarum? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2008 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 30 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acupressure; acupuncture; antihistamines; corticosteroids; corticotrophins; diazepam; dietary interventions other than ginger; domperidone; ginger; metoclopramide; ondansetron; phenothiazines; and pyridoxine (vitamin B6).

QUESTIONS

INTERVENTIONS

TREATING NAUSEA AND VOMITING

Likely to be beneficial

Unknown effectiveness

TREATING HYPEREMESIS GRAVIDARUM

Likely to be beneficial

Unknown effectiveness

Unlikely to be beneficial

Key points

- More than half of pregnant women suffer from nausea and vomiting, which typically begins by the 4th week and disappears by the 16th week of pregnancy.

  The cause of nausea and vomiting in pregnancy is unknown, but may be due to the rise in human chorionic gonadotrophin concentration.

  In 1 in 200 women, the condition progresses to hyperemesis gravidarum, which is characterised by prolonged and severe nausea and vomiting, dehydration, and weight loss.

- Ginger may reduce nausea and vomiting in pregnancy compared with placebo, although studies have given inconclusive results.

Pyridoxine may be as effective as ginger in reducing nausea, although studies have given inconsistent results about reduction of vomiting.

We don't know whether dietary interventions other than ginger are beneficial.

- P6 acupressure may reduce nausea and vomiting compared with sham acupressure, but wristbands can be difficult to use.

  We don't know whether acupressure is more effective than pyridoxine at reducing nausea or vomiting.
- We don't know whether acupuncture is more effective than sham acupuncture at reducing nausea and vomiting.
- Antihistamines may reduce nausea and vomiting compared with placebo. The antihistamine dimenhydrinate may be as effective as ginger at improving nausea at 7 days, although it seems more effective at reducing vomiting episodes in the first 2 days.
- We don't know whether phenothiazines, metoclopramide, or domperidone reduce nausea or vomiting.
- Acupressure may be more effective at reducing vomiting episodes in women with hyperemesis gravidarum compared with placebo or control (intravenous fluid therapy).
- We don't know whether acupuncture, intramuscular corticotrophin, corticosteroids, diazepam, ginger, metoclopramide, ondansetron, or other dietary interventions are effective in treating hyperemesis gravidarum.
- Corticosteroids may be more effective than metoclopramide at reducing vomiting episodes and reducing readmission to the intensive care unit in women with hyperemesis gravidarum.

DEFINITION

Nausea and vomiting are common problems in early pregnancy. Although often called “morning sickness”, nausea and vomiting can occur at any time of day and may persist throughout the day. [1] Symptoms usually begin between 4 weeks' and 7 weeks' gestation (1 study found this to be the case in 70% of affected women) [2] and disappear by 16 weeks' gestation in about 90% of women. [1] [2] [3] One study found that less than 10% of affected women suffer nausea, vomiting, or both before the first missed period. [3] Most women do not require treatment, and complete the pregnancy without any special intervention. However, if nausea and vomiting are severe and persistent, the condition can progress to hyperemesis, especially if the woman is unable to maintain adequate hydration, fluid and electrolyte balance, and nutrition. **Hyperemesis gravidarum** is a diagnosis of exclusion, characterised by prolonged and severe nausea and vomiting, dehydration, and weight loss. [1] Laboratory investigation may show ketosis, hyponatraemia, hypokalaemia, hypouricaemia, metabolic hypochloraemic alkalosis, and ketonuria.

INCIDENCE/ PREVALENCE

Nausea affects about 70% and vomiting about 60% of pregnant women. [1] The true incidence of hyperemesis gravidarum is not known. It has been documented to range from 3 in 1000 to 20 in 1000 pregnancies. However, most authors report an incidence of 1 in 200. [2]

AETIOLOGY/ RISK FACTORS

The causes of nausea and vomiting in pregnancy are unknown. One theory, that they are caused by the rise in human chorionic gonadotrophin concentration, is compatible with the natural history of the condition, its severity in pregnancies affected by hydatidiform mole, and its good prognosis (see prognosis below). [4] The cause of hyperemesis gravidarum is also uncertain. Again, endocrine and psychological factors are suspected, but evidence is inconclusive. [4] Female fetal sex has been found to be a clinical indicator of hyperemesis. [5] One prospective study found that *Helicobacter pylori* infection was more common in pregnant women with hyperemesis gravidarum than in pregnant women without hyperemesis gravidarum (number of women with positive serum *Helicobacter pylori* immunoglobulin G concentrations: 95/105 [91%] with hyperemesis gravidarum *v* 60/129 [47%] without hyperemesis gravidarum). [6] However, it was not clear whether this link was causal.

PROGNOSIS

One systematic review (search date 1988) found that nausea and vomiting were associated with a reduced risk of miscarriage (6 studies, 14,564 women; OR 0.36, 95% CI 0.32 to 0.42) but found no association with perinatal mortality. [7] Hyperemesis gravidarum is thought by some to induce nutrient partitioning in favour of the fetus, which could explain the association with improved outcome in the fetus. [8] Nausea and vomiting and hyperemesis usually improve over the course of pregnancy, but in one cross-sectional observational study 13% of women reported that nausea and vomiting persisted beyond 20 weeks' gestation. [9] Although death from nausea and vomiting during pregnancy is rare, morbidities, including Wernicke's encephalopathy, splenic avulsion, oesophageal rupture, pneumothorax, and acute tubular necrosis, have been reported. [10] [11]

AIMS OF INTERVENTION

To reduce the incidence and severity of nausea and vomiting in early pregnancy; to reduce the incidence and severity of hyperemesis gravidarum; to minimise adverse effects of treatment and possible teratogenic effects on the fetus.

OUTCOMES *All women*: **severity of nausea and vomiting episodes** (as measured on validated scales); **maternal mortality**; *in women with hyperemesis gravidarum, we also report*: **rates of admission or readmission to hospital (includes duration of hospital stay)**; *all women*: **incidence and severity of adverse effects of treatment**; and **incidence of teratogenic effects of treatments on the fetus**.

METHODS *Clinical Evidence* search and appraisal May 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2008, Embase 1980 to May 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible (e.g., acupressure trials). In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 44). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatment for nausea and vomiting in early pregnancy?**

OPTION **ACUPRESSURE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY**

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- P6 acupressure may reduce nausea and vomiting compared with sham acupressure, but wristbands can be difficult to use.
- More than half of women having P6 acupressure experience problems with using the wristband.
- We don't know whether acupressure is more effective than pyridoxine at reducing nausea or vomiting.

Benefits and harms

Acupressure versus placebo or control:

We found two systematic reviews (search date 2002, and search date from 1989 to 2005), [12] [13] one additional RCT, [14] and one subsequent RCT. [15] The first systematic review examined the effects of acupressure and acupuncture in treating nausea or vomiting in early pregnancy, and pooled results for acupressure and acupuncture together; only those results pertaining to acupressure alone have been included in this section. [12] The review identified three RCTs comparing acupressure (all 3 RCTs assessed P6 acupressure; 500 women) versus sham acupressure. [12] The second systematic review examined the effects of acupressure, acupuncture, and electrical stimulation, and identified nine RCTs comparing acupressure (3 RCTs assessing finger-applied acupressure, and 6 RCTs using wristbands) versus control (no treatment). [13] The three RCTs identified by the first review [16] [17] [18] were identified by the second review. The reviews reported on different comparisons and outcomes and so we report data from both reviews here.

Severity of nausea and vomiting

P6 acupressure compared with sham acupressure or no treatment P6 acupressure may be more effective at reducing the proportion of women who report nausea and vomiting in early pregnancy (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[19] RCT **3-armed trial**	60 women, mean gestational ages 9.6 to 10.8 weeks In review [12] The remaining arm evaluated sham acupressure	**Mean nausea score , 1 day** with P6 acupressure with no treatment	WMD –2.40 for P6 acupressure *v* no treatment 95% CI –3.78 to –1.02 P = 0.0006 for P6 acupressure *v* no treatment WMD calculated by *Clinical Evidence* contributor	○○○	P6 acupressure
[19] RCT **3-armed trial**	60 women, mean gestational ages 9.6 to 10.8 weeks In review [12] The remaining arm evaluated sham acupressure	**Mean nausea score , 6 days** with P6 acupressure with no treatment	WMD –2.00 for P6 acupressure *v* no treatment 95% CI –3.37 to –0.63 P = 0.004 for P6 acupressure *v* no treatment WMD calculated by *Clinical Evidence* contributor	○○○	P6 acupressure
[19] RCT **3-armed trial**	60 women, mean gestational ages 9.6 to 10.8 weeks In review [12] The remaining arm evaluated sham acupressure	**Mean nausea score , 14 days** with P6 acupressure with no treatment	WMD –2.30 for P6 acupressure *v* no treatment 95% CI –3.79 to –0.81 P = 0.003 for P6 acupressure *v* no treatment WMD calculated by *Clinical Evidence* contributor	○○○	P6 acupressure
[19] RCT **3-armed trial**	60 women, mean gestational ages 9.6 to 10.8 weeks In review [12] The remaining arm evaluated no treatment	**Mean nausea score , 1 day** with P6 acupressure with sham acupressure	WMD –0.40 for P6 acupressure *v* sham acupressure 95% CI –2.01 to +1.21 P = 0.63 for P6 acupressure *v* sham acupressure WMD calculated by *Clinical Evidence* contributor	⟷	Not significant
[19] RCT **3-armed trial**	60 women, mean gestational ages 9.6 to 10.8 weeks In review [12] The remaining arm evaluated no treatment	**Mean nausea score , 6 days** with P6 acupressure with sham acupressure	WMD –1.4 for P6 acupressure *v* sham acupressure 95% CI –2.89 to –0.09 P = 0.07 for P6 acupressure *v* sham acupressure WMD calculated by *Clinical Evidence* contributor	⟷	Not significant
[19] RCT **3-armed trial**	60 women, mean gestational ages 9.6 to 10.8 weeks In review [12] The remaining arm evaluated no treatment	**Mean nausea score , 14 days** with P6 acupressure with sham acupressure	WMD –1.7 for P6 acupressure *v* sham acupressure 95% CI –3.25 to –0.15 P = 0.03 for P6 acupressure *v* sham acupressure WMD calculated by *Clinical Evidence* contributor	○○○	P6 acupressure
[13] Systematic review	350 women, mean gestational ages 7.2 to 10.0 weeks Data from 1 RCT	**Proportion of women reporting nausea** 23/119 (19%) with finger acupressure 108/231 (47%) with control	RR 0.41 95% CI 0.28 to 0.60 P = 0.005 See further information on studies for details of placebo effect	●●○	finger acupressure
[13] Systematic review	273 women, mean gestational ages 8 to 11 weeks 5 RCTs in this analysis	**Proportion of women reporting nausea** 32/102 (31%) with wristband acupressure	RR 0.55 95% CI 0.38 to 0.77 P = 0.007	●○○	acupressure

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Four RCTs were of crossover design	60/106 (57%) with control	See further information on studies for details of placebo effect		
[14] RCT	138 women randomised at 13 weeks' gestation	**Frequency and severity of nausea** with acupressure given by a wristband to the P6 acupoint with sham acupressure wristband 110 women analysed Reported that acupressure reduced the frequency and severity of nausea compared with sham acupressure	Data were not reported in a way that allowed further statistical calculation		
[15] RCT **3-armed trial**	75 pregnant women suffering from nausea with or without vomiting, and who were unable to receive conventional treatment, gestational age range 5 to 12 weeks The remaining arm evaluated control treatment (women asked to complete a nausea and vomiting diary for 9 days)	**Nausea (measured using a visual analogue score: 10 cm long vertical and horizontal lines with a scale ranging from 0 = no symptoms to 10 = worst possible symptom) , 4 to 6 days** with acupressure (an acupressure band applied to acupoint P6 on days 4 to 6 and removed before going to bed) with placebo (a band applied to a sham acupressure point on the upper side of the wrists on days 4 to 6 and removed before going to bed) Absolute results not reported There were 26 women in the acupressure group, 24 women in the placebo group, and 25 women in the control group	P >0.05 for acupressure *v* placebo See further information on studies for methodological limitations	⟷	Not significant
Vomiting					
[13] Systematic review	250 women, mean gestational ages 8 to 11 weeks 5 RCTs in this analysis Three RCTs were crossover design	**Proportion of women reporting vomiting** 29/107 (27%) with wristband acupressure 58/131 (44%) with control	RR 0.45 95% CI 0.32 to 0.63 P <0.001 See further information on studies for details of placebo effect	●●○	wristband acupressure
[15] RCT **3-armed trial**	75 pregnant women suffering from nausea with or without vomiting, and who were unable to receive conventional treatment, gestational age range 5 to 12 weeks The remaining arm evaluated control treatment (women asked to complete a nausea and vomiting diary for 9 days)	**Vomiting (measured using a visual analogue score: 10 cm long vertical and horizontal lines with a scale ranging from 0 = no symptoms to 10 = worst possible symptom) , 4 to 6 days** with acupressure (an acupressure band applied to acupoint P6 on days 4 to 6 and removed before going to bed) with placebo (a band applied to a sham acupressure point on the upper side of the wrists on days 4 to 6 and removed before going to bed) Absolute results not reported There were 26 women in the acupressure group, 24 women in	P >0.05 for acupressure *v* placebo See further information on studies for methodological limitations	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		the placebo group and 25 women in the control group			
Nausea and vomiting (composite)					
[12] Systematic review	285 women 2 RCTs in this analysis	**Proportion of women reporting morning sickness (not further defined)** 37/145 (25%) with acupressure 61/140 (43%) with sham acupressure See further information on studies for details of active acupressure in each RCT	RR 0.57 95% CI 0.38 to 0.86	●○○	acupressure
[20] RCT	97 women, 8 to 12 weeks' gestation In review [12]	**Duration of nausea and vomiting** with active wristband acupressure with sham wristband acupressure	WMD –1.89 hours/12-hour cycle 95% CI –3.45 hours/12-hour cycle to –0.33 hours/12-hour cycle	○○○	active wristband acupressure
[20] RCT	97 women, 8 to 12 weeks' gestation In review [12]	**Intensity of nausea and vomiting** with active wristband acupressure with sham wristband acupressure	WMD –0.25 95% CI –0.62 to +0.12	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [12] [13] [14] [15]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [13] [14] [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] Systematic review	Number of women in this analysis not reported Data from 1 RCT	**Adverse effects** with acupressure with control The systematic review reported adverse effects in one trial, which included pain, numbness, and hand swelling (no further data reported)			

No data from the following reference on this outcome. [12] [14] [15] [19]

Acupressure versus pyridoxine (vitamin B_6):

We found one RCT comparing wristband acupressure versus pyridoxine over 7 days in women with mild to moderate nausea and vomiting in early pregnancy. [21]

Severity of nausea and vomiting

Acupressure compared with pyridoxine We don't know how acupressure and pyridoxine compare at reducing nausea or vomiting at 7 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea and vomiting					
[21] RCT	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6 to 12 weeks	**Rhodes index scores , evening of the 5th day** with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) with pyridoxine (50 mg of vitamin B_6 twice daily for 5 days) Absolute results not reported Symptoms were evaluated every 12 hours for 7 days. Women in both groups were advised to take the rescue drug dimenhydrinate in case of nausea and vomiting, and to record use. See further information on studies for full details on Rhodes index scores.	P >0.05	⟷	Not significant
[21] RCT	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6 to 12 weeks	**Rhodes index scores , evening of the 7th day after discontinuation of treatments** with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) with pyridoxine (50 mg of vitamin B_6 twice daily for 5 days) Absolute results not reported Symptoms were evaluated every 12 hours for 7 days. Women in both groups were advised to take the rescue drug dimenhydrinate in case of nausea and vomiting, and to record use See further information on studies for full details on Rhodes index scores	P >0.05	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [21]

Hospital admission/readmission rates

No data from the following reference on this outcome. [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6–12 weeks	**Adverse effects** with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) with pyridoxine (50 mg of vitamin B_6 twice daily for 5 days) The RCT reported that both acupressure and vitamin B_6 were well tolerated, and only one person complained of irritation on wearing the wristband and withdrew from treatment			

Further information on studies

[12] The first RCT included in the first systematic review compared P6 acupressure (a band applying pressure to the P6 point) versus sham treatment (a similar band with the point blunted, not exerting pressure on the P6 point). [16] Each type of band was put on each wrist in sequence. Data for the meta-analysis were taken from the third phase, when one group received active treatment to both wrists and the other placebo treatment to both wrists for 72 hours. This RCT had the largest sample size of the two RCTs included in the meta-analysis. The reliability of the randomisation in this first RCT was questioned by another paper. [22] The second RCT in the meta-analysis compared P6 acupoint acupressure versus sham acupressure (pressure applied to a point close to the right elbow), both for 5 minutes every 4 hours on four successive mornings. [17] A control group without treatment was asked only to complete a record form.

[13] Of the six RCTs assessing acupressure applied by a wristband, five RCTs used bilateral wristbands and one RCT used a unilateral wristband for 3 to 14 days. However, it is not clear whether wristbands were applied continuously or whether the results of the crossover RCTs were before or after crossover. In one RCT comparing finger-applied acupressure versus control and versus placebo, unilateral acupressure was applied by finger application on P6 acupoint for 5 to 30 minutes, four times daily or as needed for 4 to 7 days. **Placebo effect** The review also examined the placebo effects of acupressure (finger and wrist acupressure), and found that the proportion of women reporting nausea was smaller with placebo compared with control, which was of borderline significance (41/112 [37%] with placebo *v* 77/133 [58%] with control; RR 0.63, 95% CI 0.39 to 1.02; P = 0.0479). This makes the interpretation of results of the effects of acupressure difficult.

[15] The RCT found a significant reduction in the number of women reporting nausea in the treatment (P <0.001) and placebo groups (P <0.05) in days 4 to 6 compared with days 1 to 3. This makes the interpretation of results of the effects of acupressure difficult.

[21] Rhodes index scores, 8-item form: 3 items measure nausea (scores ranging from 3–15) and 5 items measure vomiting and retching (scores ranging from 5–25).

Comment: Conducting high-quality trials is difficult because nausea and vomiting tend to resolve spontaneously, and interventions are difficult to mask and control with credible placebos. In the first systematic review, results were sensitive to the method of calculation used (RR or OR), and the authors commented that the significant relative risk calculation may be an overestimate, as two RCTs that did not meet *Clinical Evidence* criteria [23] [24] found no evidence of effect. [12] In the second systematic review, there was improvement in the proportion of women who reported nausea or vomiting with all three groups. [13] The significant improvement in the placebo group makes it difficult to in-

terpret results and establish whether they were influenced by a placebo effect. It is possible that the wristbands (placebo) could produce an effect by applying pressure on the P6 acupoint or in its meridian pathway because of their uniform size and elasticity.

The subsequent RCT found acupressure had a therapeutic and placebo effect in reducing symptoms of nausea. However, this study is limited by the small number of participants in each arm. [15] In the RCT comparing acupressure and pyridoxine, women were also advised to take dimenhydrinate in the event of nausea and vomiting. Women were asked to record whether they took dimenhydrinate and, if so, how often. However, it is not clear how many women actually took dimenhydrinate or how often it was taken. It is possible that the reduction in symptoms was largely due to the effects of the rescue drug. [21]

OPTION ANTIHISTAMINES (H1 ANTAGONISTS) FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- Antihistamines may reduce nausea and vomiting compared with placebo.
- The antihistamine dimenhydrinate may be as effective as ginger at improving nausea at 7 days, although it seems more effective at reducing vomiting episodes in the first 2 days.

Benefits and harms

Antihistamines versus placebo:

We found two systematic reviews (search date 1998, 7 RCTs, 1190 women; [25] search date 2002, 6 RCTs, 571 women). [12] The two systematic reviews had five RCTs in common. Antihistamines assessed in the RCTs identified by the reviews were buclizine, dimenhydrinate, hydroxyzine, meclozine, and doxylamine.

Severity of nausea and vomiting

Antihistamines compared with placebo Antihistamines (buclizine, dimenhydrinate, doxylamine, hydroxyzine, and meclozine) may be more effective at reducing nausea and vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[12] Systematic review	571 women 6 RCTs in this analysis	**Nausea** 51/355 (14%) with antihistamines 96/216 (44%) with placebo	OR 0.20 95% CI 0.06 to 0.63 The RCTs were old and did not provide details on randomisation or concealment strategies	●●○	antihistamines
Vomiting					
[25] Systematic review	1190 women 7 RCTs in this analysis	**Treatment failure (defined as treatments that provided little or no benefit in reducing vomiting)** 84/775 (11%) with antihistamines 148/415 (36%) with untreated controls	RR 0.34 95% CI 0.27 to 0.43 Significant heterogeneity among RCTs (potentially attributed to variation in drugs in meta-analysis) The RCTs were old and did not provide details on randomisation or concealment strategies	●●○	antihistamines

Maternal mortality

No data from the following reference on this outcome. [12] [25]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	200,000 women treated between 1960 and 1991 24 controlled studies in this analysis	**Teratogenicity** with antihistamines with placebo Reported a slight decrease in risk of teratogenicity with antihistamines compared with placebo	OR 0.76 95% CI 0.60 to 0.94 Result is of borderline significance	●○○	placebo
[12] Systematic review	179 women 3 RCTs in this analysis	**Drowsiness** 23/94 (24%) with antihistamines 9/85 (11%) with placebo	RR 2.3 95% CI 1.1 to 4.7 NNH 7 95% CI 3 to 32	●●○	placebo

Antihistamines versus ginger:
See option on ginger, p 10 .

Antihistamines versus phenothiazines:
See option on phenothiazines, p 22 .

Further information on studies

Comment: A preparation combining doxylamine plus dicycloverine plus pyridoxine assessed in the second review was found to reduce nausea and vomiting. [12] However, this preparation was withdrawn from the market in several countries after publication of papers suggesting teratogenicity, although such claims have subsequently been found to be unreliable.

OPTION GINGER FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- Ginger may reduce nausea and vomiting in pregnancy compared with placebo, although studies have given inconclusive results.
- Ginger and pyridoxine may be equally effective in reducing nausea, although studies have given inconsistent results about reduction of vomiting.
- Ginger may cause heartburn and may be a gastric irritant (in quantities >6 g). In addition, inhalation of ginger dust may lead to immunoglobulin E-mediated allergy.

Benefits and harms

Ginger versus placebo:

We found one systematic review (search date 2004, 3 RCTs). [27] The review did not conduct a meta-analysis.

Severity of nausea and vomiting

Ginger compared with placebo Ginger may be more effective at reducing nausea and vomiting in early pregnancy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[28] RCT	120 women, 5.5 to 18.0 weeks' gestation In review [27]	**Nausea severity scores , each of the four treatment days** with ginger 125 mg in oral capsules taken four times daily for 4 days with placebo Absolute results reported graphically Reported that ginger significantly reduced nausea severity scores compared with placebo	Reported as significant P value not reported	○○○	ginger
Vomiting					
[29] RCT	70 women, over 17 weeks' gestation In review [27]	**Proportion of women with vomiting , 4 days** 12/32 (38%) with ginger 250 mg in oral capsules taken four times daily 23/35 (66%) with placebo	RR 0.57 95% CI 0.34 to 0.95 NNT 4 95% CI 2 to 12	●○○	ginger
[30] RCT	26 women, <13 weeks' gestation In review [27]	**Proportion of women who stopped vomiting , 6 days** 8/12 (67%) with ginger syrup (15 mL containing ginger 250 mg taken four times daily) 2/10 (20%) with placebo	RR 0.42 95% CI 0.18 to 0.98	●●○	ginger
[28] RCT	120 women, 5.5 to 18.0 weeks' gestation In review [27]	**Dry retching , first 2 days of treatment** with ginger 125 mg in oral capsules taken four times daily for 4 days with placebo Absolute results not reported Reported that ginger significantly reduced dry retching, but only on the first 2 days of treatment	Reported as significant P value not reported	○○○	ginger
[28] RCT	120 women, 5.5 to 18.0 weeks' gestation In review [27]	**Episodes of vomiting** with ginger 125 mg in oral capsules taken four times daily for 4 days with placebo Absolute results not reported Reported that ginger had no significant effect on episodes of vomiting	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[29] RCT	70 women, over 17 weeks' gestation In review [27]	**Proportion of women with improved symptoms (non-specifically described) , 7 days** 28/32 (88%) with ginger 250 mg in oral capsules taken four times daily 10/35 (29%) with placebo	RR 0.18 95% CI 0.07 to 0.45	●●●	ginger

Maternal mortality

No data from the following reference on this outcome. [27]

Hospital admission/readmission rates

No data from the following reference on this outcome. [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT	70 women, over 17 weeks' gestation In review [27]	**Spontaneous abortions** 1/32 (3%) with ginger 250 mg in oral capsules taken four times daily 3/38 (8%) with placebo	P = 0.4 RCT may have been too small to detect a clinically important difference.	⟷	Not significant
[30] RCT	26 women, <13 weeks' gestation In review [27]	**Adverse effects** with ginger syrup (15 mL containing ginger 250 mg taken four times daily) with placebo The RCT identified by the review found no adverse effects associated with ginger			
[28] RCT	120 women, 5.5 to 18.0 weeks' gestation In review [27]	**Adverse effects** with ginger 250 mg in oral capsules taken four times daily with placebo The RCT found that the most serious adverse effect was heartburn and reflux (no data reported to establish a comparison between groups)			

Ginger versus pyridoxine (vitamin B_6):

We found one systematic review (search date 2004, 2 RCTs), [27] and one subsequent RCT comparing the effectiveness of ginger versus pyridoxine in the treatment of nausea and vomiting in pregnancy. [31] The review did not conduct a meta-analysis.

Severity of nausea and vomiting

Ginger and pyridoxine compared with pyridoxine Ginger and pyridoxine may be equally effective at improving nausea and vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[32] RCT	138 women, over 16 weeks' gestation In review [27]	**Mean nausea score (severity graded using a visual analogue scale)** 1.4 with oral ginger 500 mg (provided in a capsule) for 3 days 2.0 with pyridoxine 10 mg three times daily for 3 days Both treatments improved nausea from baseline; see further information on studies for full details.	P = 0.136	⟷	Not significant
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Nausea score , change from baseline to days 7, 14, and 21 (estimated and averaged over the three time points)** –3.6 with ginger 1.05 g daily for 3 weeks –3.9 with pyridoxine 75 mg daily for 3 weeks	Mean difference +0.2 90% CI –0.3 to +0.8	⟷	Not significant
Vomiting					
[32] RCT	138 women, over 16 weeks' gestation In review [27]	**Mean vomiting score** 0.7 with oral ginger 500 mg (provided in a capsule) for 3 days 0.5 with pyridoxine 10 mg three times daily for 3 days Both treatments improved vomiting from baseline; see further information on studies for full details	P = 0.498	⟷	Not significant
[33] RCT	291 women, >16 weeks' gestation In review [27]	**Vomiting score , change from baseline to days 7, 14, and 21 (estimated and averaged over the three time points)** –0.9 with ginger 1.05 g daily for 3 weeks –0.2 with pyridoxine 75 mg daily for 3 weeks	Mean difference 0.5 90% CI 0 to 0.9	⟷	Not significant
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Retching score , change from baseline to days 7, 14, and 21 (estimated and averaged over the three time points)** –0.5 with ginger 1.05 g daily for 3 weeks –0.7 with pyridoxine 75 mg daily for 3 weeks	Mean difference 0.3 90% CI 0 to 0.6	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms (includes composite of nausea and vomiting)					
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Proportion of women symptom-free , any time during the trial** with ginger 1.05 g daily for 3 weeks with pyridoxine 75 mg daily for 3 weeks Absolute results not reported Reported that there was no significant difference between ginger and pyridoxine in the proportion of women symptom-free at any time during the trial.	Reported as not significant P value not reported	⟷	Not significant
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Women's perception of an overall reduction in their symptoms** 53% with ginger 1.05 g daily for 3 weeks 55% with pyridoxine 75 mg daily for 3 weeks Absolute numbers not reported	RR 0.97 95% CI 0.77 to 1.21	⟷	Not significant
[31] RCT	126 women with nausea and vomiting in early pregnancy who needed antiemetics, gestational age at least 16 weeks	**Mean nausea and vomiting scores (assessed using a modified form of the full Rhodes score) , 4 days** 3.3 with ginger (650 mg daily) for 4 days 2.6 with pyridoxine (25 mg three times daily) for 4 days Women in both groups took other ginger products: see further information on studies for full details See further information on studies for details of Rhodes score.	P <0.05	○○○	ginger

Maternal mortality

No data from the following reference on this outcome. [27] [31]

Hospital admission/readmission rates

No data from the following reference on this outcome. [27] [31]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT	138 women, over 16 weeks' gestation In review [27]	**Drowsiness** 17/64 (27%) with oral ginger 500 mg (provided in a capsule) 21/64 (33%) with pyridoxine 10 mg three times daily for 3 days	P = 0.439	⟷	Not significant
[32] RCT	138 women, over 16 weeks' gestation In review [27]	**Dyspepsia** 6/64 (9%) with oral ginger 500 mg (provided in a capsule) for 3 days 4/64 (6%) with pyridoxine 10 mg three times daily for 3 days	P = 0.510	⟷	Not significant
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Dry retching after swallowing** 52% with ginger 1.05 g daily for 3 weeks 56% with pyridoxine 75 mg daily for 3 weeks Absolute numbers not reported	Significance not assessed		
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Vomiting after ingestion** 2% with ginger 1.05 g daily for 3 weeks 1% with pyridoxine 75 mg daily for 3 weeks Absolute numbers not reported	Significance not assessed		
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Burning sensation** 2% with ginger 1.05 g daily for 3 weeks 2% with pyridoxine 75 mg daily for 3 weeks Absolute numbers not reported	Significance not assessed		
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Belching** 9% with ginger 1.05 g daily for 3 weeks 0% with pyridoxine 75 mg daily for 3 weeks Absolute numbers not reported	P <0.05	○○○	pyridoxine
[33] RCT	291 women, <16 weeks' gestation In review [27]	**Pregnancy outcome** with ginger 1.05 g daily for 3 weeks with pyridoxine 75 mg daily for 3 weeks There was no significant difference between ginger and pyridoxine in pregnancy outcome	Reported as not significant P value not reported	⟷	Not significant
[31] RCT	126 women with nausea and vomiting in early pregnancy who needed antiemetics, gestational age at least 16 weeks	**Adverse effects (not further specified)** 16/61 (25%) with ginger (650 mg daily) for 4 days 15/62 (24%) with pyridoxine (25 mg three times daily) for 4 days Women in both groups took other ginger products: see further information on studies for full details	P = 0.795	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Minor adverse effects reported included sedation, heartburn, headache, and arrhythmia			

Ginger versus antihistamines:

We found one RCT comparing ginger versus dimenhydrinate for 7 days. [26]

Severity of nausea and vomiting

Ginger compared with antihistamines We don't know how ginger and dimenhydrinate compare at reducing nausea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[26] RCT	170 women, gestational age <16 weeks	**Daily mean nausea scores (measured on a visual analogue scale: 10 cm vertical line with a scale ranging from 0 = no nausea to 10 = severe nausea) , days 1 to 7 of treatment** with ginger (0.5 g twice daily) for 7 days with dimenhydrinate (50 mg twice daily) for 7 days Absolute results reported graphically Nausea scores decreased in both groups	P <0.05	⟷	Not significant
Vomiting					
[26] RCT	170 women, gestational age <16 weeks	**Daily mean vomiting episodes , days 1 to 2 of treatment** with ginger (0.5 g twice daily) for 7 days with dimenhydrinate (50 mg twice daily) for 7 days Absolute results reported graphically Reported that dimenhydrinate significantly reduced daily mean vomiting episodes compared with ginger	P <0.05	○○○	dimenhydrinate
[26] RCT	170 women, gestational age <16 weeks	**Daily mean vomiting episodes , days 3 to 7 of treatment** with ginger (0.5 g twice daily) for 7 days with dimenhydrinate (50 mg twice daily) for 7 days Absolute results reported graphically	P >0.05	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [26]

Hospital admission/readmission rates

No data from the following reference on this outcome. [26]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] RCT	170 women, gestational age >16 weeks	**Episodes of drowsiness** 5/85 (6%) with ginger (0.5 g twice daily) for 7 days 66/85 (78%) with dimenhydrinate (50 mg twice daily) for 7 days	P >0.01	○○○	ginger
[26] RCT	170 women, gestational age <16 weeks	**Occurrence of heartburn** 13/85 (15%) with ginger (0.5 g twice daily) for 7 days 9/85 (11%) with dimenhydrinate (50 mg twice daily) for 7 days	P = 0.403	⟷	Not significant

Further information on studies

[29] The ginger used in the RCT was derived from fresh ginger roots and given in capsules. The authors of the RCT warn that different preparations of ginger may have different potencies and therefore different magnitudes of effects. The active ingredient that improves nausea and vomiting has not been isolated.

[31] The 3 physical symptoms measured with the Rhodes index score are defined as: episodes of nausea, duration of nausea, and number of vomits, measured on a scale ranging from 3 (lowest = slight nausea) to 15 (highest = severe nausea and vomiting). In this study, 3/61 (5%) women in the ginger group and 4/62 (7%) in the vitamin B_6 group took other ginger products, which may confound the results.

[32] The RCT identified by the systematic review [27] found that both ginger and pyridoxine significantly reduced nausea scores (from 5.0 to 3.6 with ginger *v* from 5.3 to 3.3 with pyridoxine; P <0.001 for either intervention *v* baseline) and number of vomiting episodes (from 1.9 to 1.2 with ginger *v* from 1.7 to 1.2 with pyridoxine; P <0.001 for either intervention *v* baseline) from baseline.

Comment: A review of the literature on the effects of ginger reported that ginger may cause heartburn and may be a gastric irritant (in quantities >6 g). In addition, inhalation of ginger dust may lead to immunoglobulin E-mediated allergy. [34]

OPTION PYRIDOXINE (VITAMIN B6) FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- Pyridoxine may be as effective as ginger in reducing nausea, although studies have given inconsistent results about reduction of vomiting.
- We don't know how pyridoxine and acupressure compare at reducing nausea or vomiting.

Benefits and harms

Pyridoxine (vitamin B_6) versus placebo:

We found two systematic reviews (search dates 1998 and 2002). [25] [12] Two RCTs were common to both reviews.

Severity of nausea and vomiting

Pyridoxine compared with placebo Pyridoxine may be more effective at reducing nausea but not vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[25] Systematic review	395 women 2 RCTs in this analysis	**Nausea scores** with pyridoxine with placebo	WMD –0.99 95% CI –1.47 to –0.51 The method of randomisation was unclear in one RCT	○○○	pyridoxine
[12] Systematic review	392 women 2 RCTs in this analysis	**Nausea (change in a 10-cm visual analogue scale)** with pyridoxine with placebo or no treatment	WMD 0.99 cm 95% CI 0.51 cm to 1.47 cm	○○○	pyridoxine
Vomiting					
[12] Systematic review	392 women 2 RCTs in this analysis	**Vomiting** with pyridoxine with placebo or no treatment	RR 0.76 95% CI 0.36 to 1.66	⟷	Not significant
Failure rate					
[25] Systematic review	949 women 3 RCTs in this analysis	**"Failure rates"** with pyridoxine with placebo "Failure rates" in two RCTs were defined in subjective ways and included failure to achieve resolution or a clinically important improvement in symptoms	RR 0.97 95% CI 0.78 to 1.20 The method of randomisation was unclear in one RCT	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [12] [25]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	1369 women Data from 1 cohort study	**Major fetal malformations** with pyridoxine with placebo	RR 1.05 95% CI 0.60 to 1.84	⟷	Not significant

No data from the following reference on this outcome. [12]

Pyridoxine (vitamin B_6) versus acupressure:

See option on acupressure, p 3 .

Pyridoxine (vitamin B_6) versus ginger:

See option on ginger, p 10 .

Comment: None.

OPTION ACUPUNCTURE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether acupuncture is more effective than sham acupuncture at reducing nausea and vomiting.

Benefits and harms

Acupuncture compared with sham acupuncture or no treatment:

We found two systematic reviews (search date 2002, [12] and search date from 1989 to 2005). [13] The first systematic review examined the effects of acupressure and acupuncture in treating nausea or vomiting in early pregnancy, and identified two RCTs comparing acupuncture versus sham acupuncture or no treatment. [12] The second systematic review examined the effects of acupressure, acupuncture, and electrical stimulation, and identified two RCTs comparing acupuncture versus control (no treatment) in treating nausea or vomiting in early pregnancy. [13] Two RCTs were identified by both reviews. [35] [36] We report the results of these RCTs separately, as the first review pooled results for acupressure and acupuncture together in its analyses, and the second review included studies in women with hyperemesis (which we cover as a separate question). However, both reviews reported similar results of the effects of acupuncture in women with nausea and vomiting in early pregnancy.

Severity of nausea and vomiting

Acupuncture compared with sham acupuncture or no treatment We don't know whether acupuncture is more effective at reducing nausea and retching in early pregnancy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[35] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy In review [12] [13]	**Improvement in nausea , 1 week** 13/135 (10%) with weekly traditional acupuncture for 4 weeks 4/127 (3%) with no acupuncture for 4 weeks	RR 0.93 for traditional acupuncture *v* no acupuncture 95% CI 0.88 to 0.99 See further information on studies for details on possible placebo effect	●○○	traditional acupuncture

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arms evaluated weekly PC6 acupuncture and weekly 8 sham acupuncture, both for 4 weeks.	Result between the two groups was significant after 1 week of treatment			
[35] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy In review [12] [13] The remaining arms evaluated weekly traditional acupuncture and weekly 8 sham acupuncture, both for 4 weeks	**Improvement in nausea , 2 weeks** with weekly PC6 acupuncture for 4 weeks with no acupuncture for 4 weeks Absolute results not reported Result between the two groups was significant after 2 weeks of treatment	P <0.05 for PC6 acupuncture *v* no acupuncture See further information on studies for details on possible placebo effect	○○○	PC6 acupuncture
[36] RCT	55 women, 6 to 10 weeks' gestation In review [12] [13]	**Proportion of women who reported nausea** with multisite acupuncture with sham acupuncture Absolute numbers not reported	P = 0.9	⟷	Not significant
Vomiting					
[35] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy In review [12] [13] The remaining arms evaluated weekly traditional acupuncture and weekly 8 sham acupuncture, both for 4 weeks	**Dry retching** with weekly PC6 acupuncture for 4 weeks with no acupuncture for 4 weeks	P <0.001 for PC6 acupuncture *v* no acupuncture See further information on studies for details on possible placebo effect	○○○	PC6 acupuncture

Maternal mortality

No data from the following reference on this outcome. [12] [35] [36]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [35] [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy Further report of reference [35]	**Perinatal outcome, congenital abnormalities, pregnancy complications, or other infant outcomes** with weekly traditional acupuncture for 4 weeks with weekly PC6 acupuncture for 4 weeks with weekly 8 sham acupuncture for 4 weeks with no acupuncture for 4 weeks The follow-up study found no differences between study groups in perinatal outcome, congenital abnormalities, pregnancy complications, or other infant outcomes			

No data from the following reference on this outcome. [36]

Further information on studies

[35] The RCT noted a significant improvement in nausea in all groups receiving an intervention (traditional acupuncture, PC6 acupuncture, or sham acupuncture), which makes it difficult to establish whether the results for this RCT were influenced by a placebo effect. The RCT reported that 8 sham acupuncture significantly improved nausea and dry retching compared with no acupuncture after three weeks (P <0.01). Results between the two groups were significant after 3 weeks of treatment.

Comment: The second systematic review compared three different types of acustimulation (acupressure, acupuncture, and electrical stimulation). The acupuncture intervention did not reduce nausea. It may not be acceptable for studies to compare interventions as varied as these. The number of acupuncture trials is limited for pregnant women, perhaps because it is impossible to self-administer acupuncture, and acupuncture may also be inconvenient for women experiencing chronic symptoms of nausea and vomiting. The review reported inconsistencies in frequencies of acupuncture, which varied from three times daily for 2 days to once weekly for 4 weeks. [13]

OPTION DIETARY INTERVENTIONS (OTHER THAN GINGER) FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We found no clinically important results from RCTs about the effects of dietary interventions (other than ginger) in treating women with nausea and vomiting in early pregnancy.

Benefits and harms

Dietary interventions (other than ginger):

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION DOMPERIDONE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We found no clinically important results from RCTs about the effects of domperidone in treating women with nausea and vomiting in early pregnancy.

Benefits and harms

Domperidone:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION METOCLOPRAMIDE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We found no clinically important results from RCTs about the effects of metoclopramide in treating women with nausea and vomiting in early pregnancy.

Benefits and harms

Metoclopramide:

We found no systematic review or RCTs.

Further information on studies

Comment: Studies of the teratogenic potential of metoclopramide are limited. One review of the safety of drugs for the treatment of nausea and vomiting reported no malformations among four first-trimester exposures to metoclopramide. [25] [38] The risk of tardive dyskinesia associated with long-term or high-dose use of metoclopramide has been highlighted by the FDA (http://www.fda.gov).

Clinical guide:
Metoclopramide is commonly used in clinical practice in some countries, but clinical trials are needed to evaluate its effect on nausea and vomiting in pregnancy fully.

OPTION PHENOTHIAZINES FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether phenothiazines reduce nausea or vomiting.

Benefits and harms

Phenothiazines versus placebo:

We found one systematic review (search date 2002; 2 RCTs, 300 women). [12] We also found one review (search date 1998) focusing on adverse effects. [25]

Severity of nausea and vomiting

Phenothiazines compared with placebo Phenothiazines may be no more effective at reducing nausea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[12] Systematic review	300 women 2 RCTs in this analysis	**Nausea** 34/153 (22%) with phenothiazines 97/147 (66%) with placebo	RR 0.28 95% CI 0.06 to 1.29 (random effects model) Random effects model used because of significant heterogeneity between RCTs The RCTs identified by the review were old and lacked sufficient information to appraise the quality of randomisation or allocation concealment	⟷	Not significant

No data from the following reference on this outcome. [25]

Maternal mortality

No data from the following reference on this outcome. [12]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	78,440 women Seven controlled observational trials in this analysis	**Teratogenicity** with phenothiazines with placebo	RR 1.00 95% CI 0.84 to 1.18	⟷	Not significant
[12] Systematic review	161 women Data from 1 RCT	**Teratogenicity** with phenothiazines with placebo The review gave no information on teratogenicity associated with phenothiazines. However, harms associated with different phenoth-			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		iazines vary, making it difficult to interpret a summary analysis			

Phenothiazines versus antihistamines:

We found one RCT. [39]

Severity of nausea and vomiting

Phenothiazinesompared with antihistamines We don't know how prochlorperazine (a phenothiazine) and promethazine (an antihistamine) compare at reducing nausea and vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[39] RCT **3-armed trial**	174 outpatient women in the first trimester of a singleton pregnancy The remaining arm evaluated pyridoxine (50 mg intramuscularly) plus metoclopramide (10 mg orally every 6 hours)	**Mean number of emesis episodes , day 3** 1.1 with prochlorperazine (25 mg rectal suppositories every 12 hours as needed) 0.8 with promethazine (25 mg orally every 6 hours as needed)	Significance not assessed		
Symptoms (global)					
[39] RCT **3-armed trial**	174 outpatient women in the first trimester of a singleton pregnancy The remaining arm evaluated pyridoxine (50 mg intramuscularly) plus metoclopramide (10 mg orally every 6 hours)	**Proportion of women reporting no improvement or worsening of symptoms (5-point scale ranging from "much worse" to "much better") , day 3** About 60% with prochlorperazine (25 mg rectal suppositories every 12 hours as needed) About 60% with promethazine (25 mg orally every 6 hours as needed) Absolute results reported graphically	Significance not assessed		

Maternal mortality

No data from the following reference on this outcome. [39]

Hospital admission/readmission rates

No data from the following reference on this outcome. [39]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] RCT **3-armed trial**	174 outpatient women in the first trimester of a singleton pregnancy The remaining arm evaluated pyridoxine (50 mg intramuscularly) plus metoclopramide (10 mg orally every 6 hours)	**Neonatal anomaly** 1/50 (2%) with prochlorperazine (25 mg rectal suppositories every 12 hours as needed) 0/52 (0%) with promethazine (25 mg orally every 6 hours as needed) The neonatal anomaly in the prochlorperazine group was ventricular septal defect			

Further information on studies

Comment: The trials identified by the review were old and lacked sufficient information to appraise the quality of randomisation or allocation concealment. A more conservative (random effects) analysis was used in the review because of significant heterogeneity between studies. Fixed-effect analysis found a reduction in nausea with phenothiazines, but this analysis had significant heterogeneity and should be interpreted with caution.

QUESTION What are the effects of treatments for hyperemesis gravidarum?

OPTION ACUPRESSURE FOR TREATING HYPEREMESIS GRAVIDARUM New

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- Acupressure may be more effective at reducing vomiting episodes in women with hyperemesis gravidarum compared with placebo or control (intravenous fluid therapy).

Benefits and harms

Acupressure versus placebo or control:

We found one systematic review (search date from 1989 to 2005) examining the effects of acupressure, acupuncture, and electrical stimulation in women with nausea and vomiting during pregnancy. [13] The review identified one RCT for acupressure in women with hyperemesis, but pooled data for a mixed population of women with nausea and vomiting and women with hyperemesis; hence it is not discussed further. We found one RCT. [40]

Severity of nausea and vomiting

Acupressure compared with placebo or control P6 acupressure may be more effective at reducing nausea and vomiting in women with hyperemesis gravidarum (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea and vomiting					
[40] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5 to 30 weeks	**Mean nausea and vomiting scores (assessed using modified form of full Rhodes index score) , third day after admission** 17.57 with acupressure at the Neiguan point (P6) applied using the thumb for 10 minutes three times daily for 5 to 7 days	P = 0.014 for among-group difference See further information on studies for data on placebo versus control		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		22.05 with placebo (acupressure applied around the radial pulse at the wrist) for 5 to 7 days 21.59 with control (conventional intravenous fluid therapy) for 5 to 7 days See further information on studies for details of Rhodes index score and baseline differences among patients			
[40] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5 to 30 weeks	**Mean nausea and vomiting scores , fouth day after admission** 12.48 with acupressure at the Neiguan point (P6) applied using the thumb for 10 minutes three times daily for 5 to 7 days 19.38 with placebo (acupressure applied around the radial pulse at the wrist) for 5 to 7 days 17.91 with control (conventional intravenous fluid therapy) for 5 to 7 days See further information on studies for details of Rhodes index score and baseline differences among patients	P <0.001 for among-group difference See further information on studies for data on placebo versus control		
[40] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5 to 30 weeks	**Mean nausea and vomiting scores , day of discharge** 9.22 with acupressure at the Neiguan point (P6) applied using the thumb for 10 minutes three times daily for 5 to 7 days 14.67 with placebo (acupressure applied around the radial pulse at the wrist) for 5 to 7 days 13.05 with control (conventional intravenous fluid therapy) for 5 to 7 days See further information on studies for details of Rhodes index score and baseline differences among patients	P <0.001 for among-group difference See further information on studies for data on placebo versus control		

Maternal mortality

No data from the following reference on this outcome. [40]

Hospital admission/readmission rates

No data from the following reference on this outcome. [40]

Adverse effects

No data from the following reference on this outcome. [40]

Further information on studies

[40] Nausea and vomiting were assessed using a modified form of the full Rhodes Index score (6 physical symptoms of Rhodes score: frequency of nausea and vomiting, amount of vomitus, duration of nausea, and degree of discomfort caused by nausea and vomiting measured on a scale ranging from 6 [lowest = slight nausea] to 30 [highest = severe nausea and vomiting]). The RCT reported no significant difference in mean nausea and vomiting scores among the three groups on the day of admission (mean nausea and vomiting scores: 26.26 with acupressure *v* 26.24 with placebo *v* 25.86 with control; P = 0.901 for all groups). The RCT did not assess between-group comparisons for acupressure versus either placebo or control. However, the RCT found no significant difference in nausea and vomiting scores between the placebo and control groups (P = 0.802). The study also reported no significant difference in the levels of ketonuria among the three groups on discharge (P = 0.063, absolute numbers not reported); however, levels of ketonuria were controlled more quickly in the P6 acupressure group compared with placebo or control groups during hospital stay.

Comment: Conducting high-quality trials in this area is complicated, as interventions are difficult to mask and control with credible or appropriate placebos.

OPTION ACUPUNCTURE FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether acupuncture is effective in treating hyperemesis gravidarum.

Benefits and harms

Acupuncture versus sham acupuncture:

We found one crossover RCT comparing PC6 acupuncture versus sham acupuncture. [41]

Severity of nausea and vomiting

Acupuncture compared with sham acupuncture Active PC6 acupuncture may be more effective at reducing nausea and vomiting in women with hyperemesis gravidarum (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[41] RCT **Crossover design**	50 women admitted to hospital with vomiting (all women were vomiting on the day of randomisation); gestational age range 6 to 16 weeks	**Time to resolution of nausea** with PC6 acupuncture (applied 5 mm beneath the skin on the lateral side of the forearm) with sham acupuncture (applied 1–2 mm beneath the skin on the lateral side of the forearm) Treatments were given three times daily for 30 minutes on days 1 and 2, and days 5 and 6 (after crossover) See further information on studies for data on food intake and need for IV fluids	P = 0.032	○○○	PC6 acupuncture

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[41] RCT **Crossover design**	50 women admitted to hospital with vomiting (all women were vomiting on the day of randomisation); gestational age range 6 to 16 weeks	**Proportion of women who vomited , day 4** 7/17 (41%) with PC6 acupuncture (applied 5 mm beneath the skin on the lateral side of the forearm) 12/16 (75%) with sham acupuncture (applied 1–2 mm beneath the skin on the lateral side of the forearm) Treatments were given three times daily for 30 minutes on days 1 and 2, and days 5 and 6 (after crossover) See further information on studies for data on food intake and need for IV fluids	P = 0.049	○○○	PC6 acupuncture

Maternal mortality

No data from the following reference on this outcome. [41]

Hospital admission/readmission rates

No data from the following reference on this outcome. [41]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT **Crossover design**	50 women admitted to hospital with vomiting (all women were vomiting on the day of randomisation); gestational age range 6 to 16 weeks	**Adverse effects** with PC6 acupuncture (applied 5 mm beneath the skin on the lateral side of the forearm) with sham acupuncture (applied 1–2 mm beneath the skin on the lateral side of the forearm) The RCT found no adverse effects associated with acupuncture in any women during the study			

Further information on studies

[41] The RCT found no significant differences between groups with regard to food intake and the need for intravenous fluids (reported as not significant; significance assessments not performed).

Comment: The placebo treatment (sham acupuncture) used in the RCT was superficial acupuncture on an area away from a "real" acupuncture point. Needles were inserted only 1–2 mm into the skin. The authors of the RCT state that this kind of stimulation minimises the specific effects of acupuncture. [41] However, it may not be an entirely inert placebo, as some sensory stimulation does occur.

OPTION CORTICOSTEROIDS FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether corticosteroids are effective in treating hyperemesis gravidarum.
- Corticosteroids may be more effective than metoclopramide at reducing vomiting episodes and reducing readmission to the intensive care unit in women with hyperemesis gravidarum.

Benefits and harms

Corticosteroids versus placebo:

We found two systematic reviews (search dates 1998 [25] and 2002), [12] which identified one RCT. [42] We found one subsequent RCT. [43]

Severity of nausea and vomiting

Corticosteroids compared with placebo Corticosteroids seem to be no more effective at reducing persistent vomiting in women with hyperemesis gravidarum (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[42] RCT	25 women with severe hyperemesis, mean gestational age of 10.6 weeks for prednisolone and 8.3 weeks for placebo In review [25] [12]	**Persistent vomiting** 5/12 (42%) with oral prednisolone 20 mg twice daily for 1 week 7/12 (58%) with placebo for 1 week	RR 0.71 95% CI 0.31 to 1.63 The RCT may have been too small to detect a clinically important effect.	⟷	Not significant

No data from the following reference on this outcome. [43]

Hospital admission/readmission rates

Corticosteroids compared with placebo Corticosteroids may be no more effective at reducing hospital readmission rates in women with persistent vomiting (low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[42] RCT	25 women with severe hyperemesis, mean gestational age of 10.6 weeks for prednisolone and 8.3 weeks for placebo In review [25] [12]	**Readmission to hospital** 5/12 (42%) with oral prednisolone 20 mg twice daily for 1 week 8/12 (67%) with placebo for 1 week	RR 0.63 95% CI 0.29 to 1.36 The RCT may have been too small to detect a clinically important effect	⟷	Not significant
[43] RCT	126 women, <20 weeks' gestation	**Number of women requiring readmission to hospital for hyperemesis gravidarum** 19/56 (34%) with intravenous methylprednisolone 125 mg followed by an oral prednisolone taper (40 mg for 1 day, 20 mg for	P = 0.89	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3 days, 10 mg for 3 days, 5 mg for 7 days) 19/54 (35%) with placebo (for the same regimen) All women also received promethazine 25 mg and metoclopramide 10 mg intravenously every 6 hours for 24 hours, followed by the same regimen given orally as needed until discharge.			

Maternal mortality

No data from the following reference on this outcome. [42] [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	109,602 women 8 controlled observational studies in this analysis	**Teratogenicity** with corticosteroids with control	RR 1.24 95% CI 0.97 to 1.60	⟷	Not significant
[43] RCT	126 women, <20 weeks' gestation	**Pregnancy complications** with intravenous methylprednisolone 125 mg followed by an oral prednisolone taper (40 mg for 1 day, 20 mg for 3 days, 10 mg for 3 days, 5 mg for 7 days) with placebo for the same regimen All women also received promethazine 25 mg and metoclopramide 10 mg intravenously every 6 hours for 24 hours, followed by the same regimen given orally as needed until discharge	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [42]

Corticosteroids versus antihistamines:

We found two systematic reviews (search dates 1998 [25] and 2002), [12] which identified one RCT. [44] We found one subsequent RCT. [45]

Severity of nausea and vomiting

Corticosteroids compared with antihistamines We don't know how corticosteroids and antihistamines compare at reducing nausea and vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[45] RCT	80 pregnant women, 6 to 12 weeks' gestation	**Proportion of women with severe nausea , during the first 48 hours** 20/40 (50%) with oral prednisolone 5 mg daily for 10 days 10/40 (25%) with oral promethazine 75 mg daily for 10 days	P = 0.02	○○○	promethazine
[45] RCT	80 pregnant women, 6 to 12 weeks' gestation	**Proportion of women with severe nausea , at 3 to 10 days** 14/40 (35%) with oral prednisolone 5 mg daily for 10 days 15/40 (38%) with oral promethazine 75 mg daily for 10 days	P = 0.80	⟷	Not significant
[45] RCT	80 pregnant women, 6 to 12 weeks' gestation	**Proportion of women with severe nausea , at day 17** 22/40 (56%) with oral prednisolone 5 mg daily for 10 days 27/40 (69%) with oral promethazine 75 mg daily for 10 days	P = 0.23	⟷	Not significant
Vomiting					
[44] RCT	40 women admitted to hospital at <16 weeks' gestation In review [25] [12]	**Persistence of vomiting** with oral methylprednisolone with promethazine	OR 1.56 95% CI 0.25 to 9.94	⟷	Not significant

Hospital admission/readmission rates

Methylprednisolone compared with antihistamines Methylprednisolone seems to be more effective than promethazine at reducing rates of subsequent admission to hospital, but may be associated with adverse effects (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[44] RCT	40 women admitted to hospital at <16 weeks' gestation In review [25] [12]	**Readmission to hospital** 0/17 (0%) with oral methylprednisolone 5/18 (28%) with promethazine	OR 0.11 95% CI 0.02 to 0.71	●●●	methylprednisolone

No data from the following reference on this outcome. [45]

Maternal mortality

No data from the following reference on this outcome. [44] [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT	80 pregnant women, 6 to 12 weeks' gestation	**Drowsiness , at both 48 hours and between days 3 to 10** 0/40 (0%) with oral prednisolone 5 mg daily for 10 days 6/40 (15%) with oral promethazine 75 mg daily for 10 days	P = 0.026 (at both 48 hours and between days 3–10)	○○○	prednisolone
[45] RCT	80 pregnant women, 6 to 12 weeks' gestation	**Incidence of abdominal pain , at 48 hours** 2/40 (5%) with oral prednisolone 5 mg daily for 10 days 6/40 (15%) with oral promethazine 75 mg daily for 10 days	Reported as not significant P value not reported	⟷	Not significant
[45] RCT	80 pregnant women, 6 to 12 weeks' gestation	**Incidence of abdominal pain , between days 3 to 10** 0/40 (0%) with oral prednisolone 5 mg daily for 10 days 4/40 (10%) with oral promethazine 75 mg daily for 10 days	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [44]

Corticosteroids versus metoclopramide:

We found one RCT. [46]

Severity of nausea and vomiting

Corticosteroids compared with metoclopramide Hydrocortisone seems more effective at reducing vomiting episodes in women with hyperemesis gravidarum (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[46] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Reduction of mean number of vomiting episodes , day 2** 41% with intravenous hydrocortisone (300 mg/day) for 1 week 17% with intravenous metoclopramide (10 mg three times daily) for 1 week	P <0.0001	○○○	hydrocortisone
[46] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Reduction of mean number of vomiting episodes , day 3** 72% with intravenous hydrocortisone (300 mg/day) for 1 week 51% with intravenous metoclopramide (10 mg three times daily) for 1 week	P <0.0001	○○○	hydrocortisone
[46] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Reduction of mean number of vomiting episodes , day 7** 96% with intravenous hydrocortisone (300 mg/day) for 1 week	P <0.0001	○○○	hydrocortisone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		77% with intravenous metoclopramide (10 mg three times daily) for 1 week			

Hospital admission/readmission rates

Corticosteroids compared with metoclopramide Corticosteroids seem more effective at reducing rates of readmission to the intensive care unit within 2 weeks of initial therapy in women with recurrent severe persistent vomiting (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[46] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Proportion of women readmitted to the intensive care unit for recurrence of severe persistent vomiting , within 2 weeks of initial treatment** 0/20 (0%) with intravenous hydrocortisone (300 mg/day) for 1 week 6/20 (30%) with intravenous metoclopramide (10 mg three times daily) for 1 week	P <0.0001	◌◌◌	hydrocortisone

Maternal mortality

No data from the following reference on this outcome. [46]

Adverse effects

No data from the following reference on this outcome. [46]

Further information on studies

Comment: **Clinical guide:**
The rates of spontaneous resolution of symptoms in control groups were high. The possible benefit of methylprednisolone in preventing subsequent admission to hospital must be balanced against possible adverse effects of steroids given in the first trimester of pregnancy. Clinical judgement would be more important in specific situations as there are no reports of adverse effects; however, these may be rare but serious.

OPTION CORTICOTROPHINS FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether intramuscular corticotrophin is effective in treating hyperemesis gravidarum.

Benefits and harms

Corticotrophins versus placebo:

We found two systematic reviews (search dates 1998 [25] and 2002) [12] of corticotrophins in hyperemesis gravidarum, which identified the same sole RCT. [47]

Severity of nausea and vomiting

Corticotrophins compared with placebo Intramuscular corticotrophin may be no more effective at improving nausea scores in women with hyperemesis gravidarum, but we don't know whether it is more effective at reducing vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[47] RCT	32 women, gestational ages and severity of hyperemesis not reported In review [25] [12]	**Nausea relief scores (measured on a scale ranging from 15 = lack of nausea to 20 = worst possible hyperemesis)** with intramuscular corticotrophin (adrenocorticotrophic hormone) 0.5 mg with placebo Absolute results not reported Women remained in hospital for at least 10 days	WMD relief score +0.6 95% CI –1.65 to +2.85	⟷	Not significant
Vomiting					
[47] RCT	32 women, gestational ages and severity of hyperemesis not reported In review [25] [12]	**Time from starting treatment to stopping vomiting** with intramuscular corticotrophin (adrenocorticotrophic hormone) 0.5 mg with placebo Absolute results not reported Reported that there was no difference in time from starting treatment to stopping vomiting between groups All women stopped vomiting while in hospital Women remained in hospital for at least 10 days	Significance not assessed		

Hospital admission/readmission rates

Corticotrophins compared with placebo Intramuscular corticotrophin may be no more effective at reducing hospital readmission rates in women with hyperemesis gravidarum (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[47] RCT	32 women, gestational ages and severity of hyperemesis not reported	**Number of readmissions to hospital** with intramuscular corticotrophin (adrenocorticotrophic hormone) 0.5 mg with placebo Reported that there was no difference between groups in the number of readmissions to hospital	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Women initially remained in hospital for at least 10 days			

Maternal mortality

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	32 women Data from 1 RCT	**Adverse effects** with corticotrophin with placebo The first systematic review reported no adverse effects associated with corticotrophins			

No data from the following reference on this outcome. [12]

Further information on studies

Comment: None.

OPTION DIAZEPAM FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether diazepam is effective in treating hyperemesis gravidarum.

Benefits and harms

Diazepam versus placebo:

We found one systematic review (search date 2002, 1 RCT). [12]

Severity of nausea and vomiting

Corticotrophins compared with placebo We don't know whether diazepam is more effective at reducing the severity of nausea and vomiting in women with hyperemesis gravidarum (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[12] Systematic review	50 women admitted to hospital Data from 1 RCT	**Persistence of vomiting , 2 days** with intravenous diazepam 20 mg daily followed by oral diazepam 5 mg twice daily with intravenous fluid followed by placebo All women were given IV fluids until symptoms settled. IV fluids contained a multivitamin preparation	OR 0.64 95% CI 0.10 to 4.19 Assessment not clearly reported The trial was too small to draw reliable conclusions	⟷	Not significant

Hospital admission/readmission rates

Corticotrophins compared with placebo We don't know whether diazepam is more effective at reducing readmissions to hospital in women with hyperemesis gravidarum (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[12] Systematic review	50 women admitted to hospital Data from 1 RCT	**Readmission to hospital** 4% with intravenous diazepam 20 mg daily followed by oral diazepam 5 mg twice daily 27% with intravenous fluid followed by placebo Absolute numbers not reported All women were given IV fluids until symptoms settled. IV fluids contained a multivitamin preparation	Significance not assessed The trial was too small to draw reliable conclusions.		

Maternal mortality

No data from the following reference on this outcome. [12]

Adverse effects

No data from the following reference on this outcome. [12]

Further information on studies

Comment: The rate of resolution in the control group was high, and the effects of the vitamins used in the RCT are unknown.

OPTION DIETARY INTERVENTIONS (OTHER THAN GINGER) FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether dietary interventions are effective in treating hyperemesis gravidarum.

Benefits and harms

Carob seed powder plus calcium lactate versus placebo:

We found no systematic review. We found one crossover RCT comparing 1 g daily of a powder containing 96.5% carob seed flour plus 3.5% calcium lactate versus placebo for 3 weeks. [48]

Severity of nausea and vomiting

Carob seed powder plus calcium lactate compared with placebo We don't know whether dietary supplementation with carob seed flour plus calcium lactate is more effective at relieving vomiting in women with hyperemesis gravidarum (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[48] RCT **Crossover design**	43 women	**Relief of vomiting (subjective improvement)** 20/34 (59%) with 1 g daily of a powder containing 96.5% carob seed flour plus 3.5% calcium lactate for 3 weeks 18/36 (50%) with placebo for 3 weeks	RR 1.18 95% CI 0.82 to 1.70 The RCT was conducted in 1966, so it is unclear whether the composition of carob seed flour now commercially available is the same as was used in this RCT	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [48]

Hospital admission/readmission rates

No data from the following reference on this outcome. [48]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[48] RCT **Crossover design**	43 women	**Adverse effects** with 1 g daily of a powder containing 96.5% carob seed flour plus 3.5% calcium lactate for 3 weeks with placebo for 3 weeks The RCT found no adverse effects associated with carob seed flour			

Further information on studies

Comment: None.

OPTION GINGER FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether ginger is effective in treating hyperemesis gravidarum.

Benefits and harms

Ginger versus placebo:

We found two systematic reviews (search dates 2002 [12] and 2004). [27] Both reviews identified the same crossover RCT. [49]

Severity of nausea and vomiting

Ginger compared with placebo We don't know whether ginger is more effective at reducing hyperemesis scores at 4 days in women with hyperemesis gravidarum (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hyperemesis gravidarum					
[49] RCT **Crossover design**	30 women admitted to hospital with hyperemesis gravidarum In review [12] [27]	**Hyperemesis score (evaluates degree of nausea and vomiting, weight gain, and participant-reported symptom relief; higher score indicates fewer symptoms) , after 4 days (before crossover)** 4.1 with ginger 250 mg in oral capsules taken four times daily 0.9 with placebo 27 women included in the analysis	P = 0.035 in RCT WMD +3.15 (as calculated by review) [12] 95% CI –0.92 to +7.22 The RCT was too small to allow reliable conclusions		

Maternal mortality

No data from the following reference on this outcome. [49]

Hospital admission/readmission rates

No data from the following reference on this outcome. [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[49] RCT **Crossover design**	30 women admitted to hospital with hyperemesis gravidarum, 27 women included in the analysis In review [12] [27]	**Adverse effects** with ginger 250 mg in oral capsules taken four times daily with placebo The RCT reported no adverse effects associated with ginger			

Comment: None.

OPTION METOCLOPRAMIDE FOR TREATING HYPEREMESIS GRAVIDARUM New

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether metoclopramide is effective in treating hyperemesis gravidarum, as we found no clinically important results from RCTs.

Benefits and harms

Metoclopramide versus placebo:

We found no systematic review or RCTs.

Metoclopramide versus corticosteroids:

See option on corticosteroids, p 29 .

Further information on studies

Comment: Studies of the teratogenic potential of metoclopramide are limited. One review of the safety of drugs for the treatment of nausea and vomiting reported no malformations among four first-trimester exposures to metoclopramide. [25] [38] The risk of tardive dyskinesia associated with long-term or high-dose use of metoclopramide has been highlighted by the FDA (http://www.fda.gov).

Clinical guide:
Metoclopramide is commonly used in clinical practice in some countries, but clinical trials are needed to fully evaluate its effects on nausea and vomiting in pregnancy.

OPTION ONDANSETRON FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 44 .
- We don't know whether ondansetron is effective in treating hyperemesis gravidarum.

Benefits and harms

Ondansetron versus placebo:

We found no systematic review or RCTs.

Ondansetron versus antihistamines:

We found one systematic review (search date 2002, 1 RCT, [50] 30 women admitted to hospital). [12]

Severity of nausea and vomiting

Ondansetron compared with antihistamines Ondansetron and promethazine seem to be equally effective at 48 hours at reducing the proportion of women with hyperemesis gravidarum (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[50] RCT	30 women admitted to hospital In review [12]	**Proportion of women vomiting, 48 hours** 1/15 (7%) with ondansetron 10 mg in 50 mL intravenous solution over 30 minutes 3/15 (20%) with promethazine 50 mg in 50 mL intravenous solution over 30 minutes After infusion, subsequent doses of both drugs were given as needed every 8 hours until the recipient was able to eat a bland diet	RR 0.33 95% CI 0.04 to 2.85 The RCT was too small to draw reliable conclusions	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [50]

Hospital admission/readmission rates

No data from the following reference on this outcome. [50]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[50] RCT	30 women admitted to hospital In review [12]	**Sedation** 0/15 (0%) with ondansetron 10 mg in 50 mL intravenous solution over 30 minutes 8/15 (53%) with promethazine 50 mg in 50 mL intravenous solution over 30 minutes After infusion, subsequent doses of both drugs were given as needed every 8 hours until the recipient was able to eat a bland diet.	P = 0.002	○○○	ondansetron

No data from the following reference on this outcome. [12]

Further information on studies

Comment: None.

GLOSSARY

Acupressure Pressure applied to a specific point of the body. It does not require needles and can be given by patients themselves. Commercial products available include an elastic band to fit around the wrist with a plastic disc to apply pressure at the P6 point.

Hydatidiform mole A condition in which there is abnormal cystic development of the placenta. The uterus is often large for the duration of pregnancy and there may be vaginal bleeding, lack of fetal movement and fetal heart sounds, and severe nausea and vomiting. Rarer, but important, complications include haemorrhage, intrauterine infection, hypertension, and persistent gestational trophoblastic disease, which may infiltrate local tissues or metastasise to distant sites.

Metabolic hypochloraemic alkalosis Excess base alkali in the body fluids caused by chloride loss.

P6 acupressure Pressure is applied at the P6 (Neiguan) point on the volar aspect of the wrist.

PC6 acupuncture The needle is applied at the PC6 point located near to the wrist crease.

Wernicke's encephalopathy A severe syndrome caused by a deficiency of thiamine (vitamin B1). It is usually associated with excessive alcohol abuse and is characterised by abnormal eye movements, confusion, and loss of short term memory and muscular coordination.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Acupressure for treating hyperemesis gravidarum: One RCT added, which found that acupressure was more effective at reducing nausea and vomiting episodes compared with placebo and control (conventional intravenous fluid). [40] Categorised as Likely to be beneficial.

Metoclopramide for treating hyperemesis gravidarum: One RCT found that metoclopramide was less effective at reducing vomiting episodes and readmission to the intensive care unit compared with corticosteroids. [46] Other drugs and interventions may be more useful. Categorised as Unlikely to be beneficial.

Acupressure for treating nausea and vomiting in early pregnancy: One systematic review [13] and two RCTs added. [15] [21] The systematic review found that acupressure applied as a wristband reduced the proportion of women reporting nausea and vomiting compared with control. One RCT found no significant difference between acupressure and placebo in the number of women who reported nausea and vomiting. [15] The RCT comparing acupressure and pyridoxine found no significant difference between the two treatments in Rhodes index scores. [21] Categorisation unchanged (Likely to be beneficial).

Acupuncture for treating nausea and vomiting in early pregnancy: One systematic review added. [13] The review identified the same RCTs already reported and came to similar conclusions. Categorisation unchanged (Unknown effectiveness).

Antihistamines (H_1 antagonists) for treating nausea and vomiting in early pregnancy: One RCT added. [26] The RCT found that the antihistamine dimenhydrinate improved vomiting for the first 2 days compared with ginger, but there was no significant difference at days 3 to 7. It also found no significant difference in nausea scores between the two groups. Categorisation unchanged (Likely to be beneficial).

Ginger for treating nausea and vomiting in early pregnancy: Two RCTs added. [26] [31] One RCT found that ginger was more effective at reducing nausea and vomiting scores compared with pyridoxine. [31] One RCT comparing ginger and antihistamines found that dimenhydrinate improved vomiting for the first 2 days compared with ginger, but there was no significant difference at days 3 to 7. It also found no significant difference in nausea scores between the two groups. [26] Categorisation unchanged (Likely to be beneficial).

Pyridoxine (vitamin B_6) for treating nausea and vomiting in early pregnancy: Two RCTs added. [15] [31] The RCT comparing acupressure and pyridoxine found no significant difference between the two treatments in Rhodes index scores. The other RCT found that pyridoxine was less effective compared with ginger at reducing nausea and vomiting scores. Categorisation unchanged (Likely to be beneficial).

REFERENCES

1. Nelson-Piercy C. Treatment of nausea and vomiting in pregnancy. When should it be treated and what can be safely taken? *Drug Saf* 1998;19:155–164.[PubMed]
2. Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. *Am J Perinatol* 2000;17:207–218.[PubMed]
3. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract* 1993;43:245–248.[PubMed]
4. Baron TH, Ramirez B, Richter JE. Gastrointestinal motility disorders during pregnancy. *Ann Intern Med* 1993;118:366–375.[PubMed]
5. Tan PC, Jacob R, Quek KF, et al. The fetal sex ratio and metabolic, biochemical, haematological and clinical indicators of severity of hyperemesis gravidarum. *BJOG* 2006;113:733–737.[PubMed]
6. Philip B. Hyperemesis gravidarum: literature review. *WMJ* 2003;102:46–51. Search date 2001; primary source Medline.
7. Weigel MM, Weigel RM. Nausea and vomiting of early pregnancy and pregnancy outcome. A meta-analytical review. *Br J Obstet Gynaecol* 1989;96:1312–1318. Search date 1988; primary sources Medline and hand searches of references cited in identified articles.[PubMed]
8. Furneaux EC, Langley-Evans AJ, Langley-Evans SC. Nausea and vomiting of pregnancy: endocrine basis and contribution to pregnancy outcome. *Obstet Gynecol Surv* 2001;56:775–782.[PubMed]
9. Whitehead SA, Andrews PLR, Chamberlain GVP. Characterisation of nausea and vomiting in early pregnancy: a survey of 1000 women. *J Obstet Gynaecol* 1992;12:364–369.
10. Selitsky T, Chandra P, Schiavello HJ. Wernicke's encephalopathy with hyperemesis and ketoacidosis. *Obstet Gynecol* 2006;107:486–490.[PubMed]
11. American College of Obstetricians and Gynecologists. ACOG practice bulletin: nausea and vomiting of pregnancy. *Obstet Gynecol* 2004;103:803–814.[PubMed]
12. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. In: The Cochrane Library, Issue 2, 2008. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.[PubMed]
13. Helmreich RJ, Shiao SY, Dune LS. Meta-analysis of acustimulation effects on nausea and vomiting in pregnant women. *Explore (NY)* 2006;2:412–421.[PubMed]
14. Steele NM, French J, Gatherer-Boyles J, et al. Effect of acupressure by Sea-Bands on nausea and vomiting of pregnancy. *J Obstet Gynecol Neonatal Nurs* 2001;30:61–70.[PubMed]
15. Can Gurkan O, Arslan H. Effect of acupressure on nausea and vomiting during pregnancy. *Complement Ther Clin Pract* 2008;14:46–52.[PubMed]
16. Dundee JW, Sourial FBR, Ghaly RG, et al. P6 acupressure reduces morning sickness. *J R Soc Med* 1988;81:456–457.[PubMed]
17. De Aloysio D, Penacchioni P. Morning sickness control in early pregnancy by Neiguan point acupressure. *Obstet Gynecol* 1992;80:852–854.[PubMed]
18. Belluomini J, Litt RC, Lee KA, et al. Acupressure for nausea and vomiting of pregnancy: a randomized, blinded study. *Obstet Gynecol* 1994; 84: 245-248.[PubMed]
19. Werntoft E, Dykes AK. Effect of acupressure on nausea and vomiting during pregnancy: a randomised controlled, pilot study. *J Reprod Med* 2001;46:835–839.[PubMed]
20. Norheim AJ, Pedersen EJ, Fønnebø V, et al. Acupressure treatment of morning sickness in pregnancy: a randomised, double-blind, placebo-controlled study. *Scand J Prim Health Care* 2001;19:43–47.[PubMed]
21. Jamigorn M, Phupong V. Acupressure and vitamin B6 to relieve nausea and vomiting in pregnancy: a randomized study. *Arch Gynecol Obstet* 2007;276:245–249.[PubMed]
22. Dundee J, McMillan C. Some problems encountered in the scientific evaluation of acupuncture emesis. *Acupunct Med* 1992;10:2–8.
23. Belluomini J, Litt RC, Lee KA, et al. Acupressure for nausea and vomiting of pregnancy: a randomized, blinded study. *Obstet Gynecol* 1994;84:245–248.[PubMed]
24. O'Brien B, Relyea MJ, Taerum T. Efficacy of P6 acupressure in the treatment of nausea and vomiting during pregnancy. *Am J Obstet Gynecol* 1996;174:708–715.[PubMed]
25. Mazzotta P, Magee LA. A risk–benefit assessment of pharmacological and non-pharmacological treatments for nausea and vomiting of pregnancy. *Drugs* 2000;59:781–800. Search date 1998; primary sources Medline, Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews, hand searches of bibliographies of retrieved papers, standard toxicology text (Drugs in Pregnancy and Lactation), and personal contact with pharmaceutical companies, researchers, and clinicians in the fields of pharmacology, toxicology, obstetrics, and paediatrics.[PubMed]
26. Pongrojpaw D, Somprasit C, Chanthasenanont A. A randomized comparison of ginger and dimenhydrinate in the treatment of nausea and vomiting in pregnancy. *J Med Assoc Thai* 2007;90:1703–1709.[PubMed]
27. Borrelli F, Capasso R, Aviello G, et al. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. *Obstet Gynecol* 2005;105:849–856. Search date 2004; primary sources Medline, Embase, The Cochrane Library, reference lists, manufacturers of preparations containing ginger, and websites providing information to pregnant women. [PubMed]
28. Willetts K, Ekangaki A, Eden J. Effect of a ginger extract on pregnancy-induced nausea: a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2003;43:139–144.[PubMed]
29. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. *Obstet Gynaecol* 97;2001:577–582.
30. Keating A, Chez RA. Ginger syrup as an antiemetic in early pregnancy. *Altern Ther Health Med* 2002;8:89–91.[PubMed]
31. Chittumma P, Kaewkiattikun K, Wiriyasiriwach B. Comparison of the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in early pregnancy: a randomized double-blind controlled trial. *J Med Assoc Thai* 2007;90:15–20.[PubMed]
32. Sripramote M, Lekhyananda N. A randomized comparison of ginger and vitamin B6 in the treatment of nausea and vomiting of pregnancy. *J Med Assoc Thai* 2003;86:846–853.[PubMed]
33. Smith C, Crowther C, Willson K, et al. A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy. *Obstet Gynecol* 2004;103:639–645.[PubMed]
34. Chrubasik S, Pittler MH, Roufogalis BD. *Zingiberis rhizoma:* a comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* 2005;12:684–701.[PubMed]
35. Smith C, Crowther C, Beilby J. Acupuncture to treat nausea and vomiting in early pregnancy: a randomized controlled trial. *Birth* 2002;29:1–9.[PubMed]
36. Knight B, Mudge C, Openshaw S, et al. Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial. *Obstet Gynecol* 2001;97:184–188.[PubMed]
37. Smith C, Crowther C, Beilby J. Pregnancy outcome following women's participation in a randomised controlled trial of acupuncture to treat nausea and vomiting in early pregnancy. Complementary Therapies in Medicine. 2002; 10: 78-83.[PubMed]
38. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol* 2002;186:S256–S261.[PubMed]
39. Bsat FA, Hoffman DE, Seubert DE. Comparison of three outpatient regimens in the management of nausea and vomiting in pregnancy. *J Perinatol* 2003;23:531–535.[PubMed]
40. Shin HS, Song YA, Seo S. Effect of Nei-Guan point (P6) acupressure on ketonuria levels, nausea and vomiting in women with hyperemesis gravidarum. *J Adv Nurs* 2007;59:510–519.[PubMed]
41. Carlsson CP, Axemo P, Bodin A, et al. Manual acupuncture reduces hyperemesis gravidarum: a placebo-controlled, randomized, single-blind, crossover study. *J Pain Symptom Manage* 2000;20:273–279.[PubMed]
42. Nelson-Piercy C, Fayers P, de Swiet M. Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. *Br J Obstet Gynaecol* 2001;108:9–15.[PubMed]
43. Yost NP, McIntire DD, Wians FH Jr, et al. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. *Obstet Gynecol* 2003;102:1250–1254.[PubMed]
44. Safari HR, Fassett MJ, Souter IC, et al. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study. *Am J Obstet Gynecol* 1998;179:921–924.[PubMed]
45. Ziaei S, Hosseiney FS, Faghihzadeh S. The efficacy low dose of prednisolone in the treatment of hyperemesis gravidarum. *Acta Obstet Gynecol Scand* 2004;83:272–275.[PubMed]
46. Bondok RS, El Sharnouby NM, Eid HE, et al. Pulsed steroid therapy is an effective treatment for intractable hyperemesis gravidarum. *Crit Care Med* 2006;34:2781–2783.[PubMed]
47. Ylikorkala O, Kauppila A, Ollanketo ML. Intramuscular ACTH or placebo in the treatment of hyperemesis gravidarum. *Acta Obstet Gynecol Scand* 1979;58:453–455.[PubMed]
48. General Practitioner's Research Group. Hyperemesis treated with a pharmacologically inert compound. *Practitioner* 1966;196:711–714.[PubMed]
49. Fischer-Rasmussen W, Kjaer SK, Dahl C, et al. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol* 1991;38:19–24. [PubMed]
50. Sullivan CA, Johnson CA, Roach H, et al. A pilot study of intravenous ondansetron for hyperemesis gravidarum. *Am J Obstet Gynecol* 1996;174:1565–1568.[PubMed]

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Disclaimer

GRADE **Evaluation of interventions for Nausea and vomiting in early pregnancy.**

Important outcomes	Hospital admission/readmission rates, Maternal mortality, Severity of nausea and vomiting								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatment for nausea and vomiting in early pregnancy?									
at least 14 (at least 1853 women) [12] [13] [14] [15]	Severity of nausea and vomiting	Acupressure versus placebo or control	4	–2	–1	–1	0	Very low	Quality points deducted for randomisation flaws and other methodological flaws. Consistency point deducted for conflicting results. Directness point deducted for inclusion of different interventions
1 (66) [21]	Severity of nausea and vomiting	Acupressure versus pyridoxine (vitamin B6)	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of other interventions
at least 7 (at least 1190 women) [12] [25]	Severity of nausea and vomiting	Antihistamines versus placebo	4	–1	–1	0	0	Low	Quality point deducted for randomisation flaws. Consistency point deducted for heterogeneity among studies
3 (216) [27]	Severity of nausea and vomiting	Ginger versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for uncertainty about intervention
3 (552) [27] [31]	Severity of nausea and vomiting	Ginger versus pyridoxine (vitamin B6)	4	0	0	–2	0	Low	Directness points deducted for uncertainty about intervention and uncertainty about effects of taking additional ginger products
1 (170) [26]	Severity of nausea and vomiting	Ginger versus antihistamines	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for different results at different endpoints
5 (787) [12] [25]	Severity of nausea and vomiting	Pyridoxine (vitamin B6) versus placebo	4	–2	0	0	0	Low	Quality points deducted for randomisation issues and uncertain diagnosis or outcome
2 (648) [12]	Severity of nausea and vomiting	Acupuncture compared with sham acupuncture or no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about benefit
2 (300) [12]	Severity of nausea and vomiting	Phenothiazines versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for uncertainty about randomisation and allocation. Consistency point deducted for heterogeneity among studies
1 (174) [39]	Severity of nausea and vomiting	Phenothiazines versus antihistamines	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of treatments for hyperemesis gravidarum?									
1 (66) [40]	Severity of nausea and vomiting	Acupressure versus placebo or control	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between interventions
1 (50) [41]	Severity of nausea and vomiting	Acupuncture versus sham acupuncture	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (24) [42]	Severity of nausea and vomiting	Corticosteroids versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Hospital admission/readmission rates, Maternal mortality, Severity of nausea and vomiting								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (150) [42] [43]	Hospital admission/readmission rates	Corticosteroids versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of other interventions
2 (120) [44] [45]	Severity of nausea and vomiting	Corticosteroids versus antihistamines	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results at different endpoints
1 (40) [44]	Hospital admission/readmission rates	Corticosteroids versus antihistamines	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [46]	Severity of nausea and vomiting	Corticosteroids versus metoclopramide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [46]	Hospital admission/readmission rates	Corticosteroids versus metoclopramide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (32) [47]	Severity of nausea and vomiting	Corticotrophins versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (32) [47]	Hospital admission/readmission rates	Corticotrophins versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (50) [12]	Severity of nausea and vomiting	Diazepam versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting. Directness point deducted for uncertainty about effect of other interventions
1 (50) [12]	Hospital admission/readmission rates	Diazepam versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting. Directness point deducted for uncertainty about effect of other interventions
1 (43) [48]	Severity of nausea and vomiting	Carob seed powder plus calcium lactate versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about composition of intervention
1 (30) [49]	Severity of nausea and vomiting	Ginger versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for conflicting results on analysis. Directness point deducted for composite outcome
1 (30) [50]	Severity of nausea and vomiting	Ondansetron versus antihistamines	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.